REMARKS

After entry of this amendment claims 1-16 and 18-20 are pending, of which claim 6 is withdrawn. The claims have been amended without prejudice or disclaimer. Support is found *inter alia* in the original claims. Claims 1-3 and 7-8 have been amended without prejudice or disclaimer and also find support in original claims 1-3, 7-8, and in the specification at page 10 line 23 through page 11 line 44. Claim 9 has been amended to correct an inadvertent typographical error. No new matter has been added.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7-16 and 18-20 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement and for lack of an enabling disclosure. Applicants respectfully disagree and traverse the rejections.

Enablement Rejection

The Examiner rejects the claims for lack of enablement, alleging that the specification is only enabled for the promoter sequence of SEQ ID NO: 1. Applicants respectfully disagree. However, in order to expedite prosecution, the claims have been amended without prejudice or disclaimer and relate to using a promoter sequence or a fragment thereof for directing expression of a further nucleic acid sequence in carbohydrate-storing sink tissue of plants, but essentially not in source tissues. Applicants respectfully request reconsideration in light of the amendment and for the following reasons.

The Examiner has interpreted the promoter sequence to be as little as 2 base pairs or merely a TATAA box (see Office Action, page 2, last sentence). Applicants respectfully disagree with the Examiner's characterization. For clarification the claims are amended without disclaimer or prejudice and are directed to a functional promoter or functional fragment thereof which directs expression of a nucleic acid to carbohydrate-storing sink tissue of plants. Thus, the promoter or fragment thereof must be capable of directing expression to carbohydrate-storing sink tissue, but essentially not in source tissue. A promoter comprising only a two base pair sequence or a TATAA box would not meet the limitations recited in the claims.

The Examiner alleges that the specification does not provide guidance for any fragment smaller than SEQ ID NO: 1 or any sequence variants of SEQ ID NO: 1. The Examiner argues that the function of promoter fragments and sequence variants in transgenic plants and deletion analysis of promoters is unpredictable, citing Kim *et al.* (hereinafter "Kim") and Donald *et al.* (hereinafter "Donald"), respectively. The Examiner further alleges that the function of promoter fragments and sequence variants in transgenic plants is unpredictable when the promoter function is regulated by conditional elements, citing Dolferus *et al.* (hereinafter "Dolferus"). The Examiner concludes that undue experimentation would be required to develop and evaluate all promoter-effective molecules from Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase as claimed. It is respectfully submitted that Kim, Donald, and Dolferus do not support the position alleged by the Examiner. Rather, these references support enablement and show that the essential promoter elements occupy only a small fraction of a promoter sequence, which in turn implies that the vast majority of a promoter sequence may be modified or deleted without affecting promoter activity.

Specifically, the Examiner argues that Kim shows that mutation of a single nucleotide significantly altered the strength of expression, while deletions in other regions of the promoter completely eliminated function. However, Kim actually supports enablement. The mutation described in Kim was not a random mutation of a promoter sequence, but a mutational analysis of an essential part of 30 nucleotides of the *nos* promoter (page 106 and 107, first paragraphs right column). This short nucleotide sequence selected by Kim contains two hexamer motifs surrounding a spacer region of 8 nucleotides (page 108, Table 1). By replacing this essential part with mutated oligomers (page 107, full right column) Kim demonstrated the importance of the two hexamer sequence elements. Kim thus found that promoters consist of essential elements which can readily be identified with the help of deletion experiments in combination with a standard search for sequence motifs. The symmetric structure of the hexamers identified by Kim is readily visualized by a person skilled in the art. A symmetric structure consisting of a spacer region surrounded by hexamers or palindromes can be identified by pure sequence analysis with or without the help of computer algorithms. Furthermore, Kim supports the view that even in these sequence elements mutations do not necessarily abolish promoter activity. To the contrary, Kim shows that only 20 nucleotides out of 30 identified by deletion analysis are important for

promoter activity. Kim also shows that mutations in the 20 nucleotides left, like changing one hexamer of the sequence to a palindrome, does improve promoter activity. Changing the spacer region to a symmetric sequence does improve the promoter activity even further (page 110, Table 3, *nos*, 128-CG and *ocs*). Thus Kim discloses that a 30 base pair element can be narrowed down to 20 nucleotides, of which 10 can be mutated, loosing promoter activity only in two constructs. Thus Kim has demonstrated that even in this small element of 30 base pairs, shown to be essential for promoter activity, more than 30% of the bases can be mutated without loosing the activity.

The Examiner cites Donald to support the allegation that promoter deletion analysis is unpredictable. Rather Donald defined a 196 bp long fragment of the *Arabidopsis thaliana* rbc8-1A promoter as being essential and sufficient for promoter activity (page 1717, abstract). Donald also showed that this promoter fragment had the capacity to direct expression independent of its orientation and relative position in the *Adh* promoter. Further sequence analysis showed that this promoter fragment contained further promoter elements necessary for its activity (page 1717 abstract and page 1720, Figure 3). Donald also disclosed that the expression pattern of the promoter fragment can be influenced by other active promoter fragments and enhancing elements contained in the CaMV promoter fragment and the *Adh* promoter used by Donald (page 1724, last paragraph). This does not show that promoter deletion analysis is unpredictable. Rather Donald showed that active fragments and elements from other promoters could restore activity following mutations in essential boxes (see abstract and page 1724). Donald also demonstrated that a promoter fragment identified by deletion analysis can be used independent of its orientation and relative position and still preserve its activity, as long as particular sequence elements like the G-, I- or GT-box are not destroyed by mutation (page 1724, last paragraph). Those boxes have a size of only 12 to 14 base pairs (page 1720, Figure 3) and represent only a minor part of the rbcS-1A LRE sequence of 196 base pairs. Moreover, as in Kim, the mutations described in Donald were site-specific mutations in conserved sequences and not random mutations (see abstract).

Dolferus discloses a detailed analysis of an inducible promoter of about 1 kb in length from *Arabidopsis*. By using only 5 deletion constructs, Dolferus showed that the promoter contained four different regions (regions I, II, III and IV), of which region I was responsible for

preventing noninduced expression. Region II contained a positive regulatory element necessary for high level expression. Regions III and IV were the most critical regions for promoter activity. These two regions contained five small promoter elements (page 1075, abstract). Further mutational analysis of these small promoter elements, having a size between 7 and 28 base pairs, showed that only four of them were necessary for preserving promoter activity (page 1085, Figure 6). Dolferus by a simple sequence analysis identified critical regions of the promoter which when mutated affected promoter activity. Analogous to the disclosure of Kim and Donald, the mutations done by Dolferus were not random. This strategy is clearly stated by Dolferus "Site-specific mutagenesis (Kunkel et al., 1987) was used to introduce mutations at four specific regions of the CADH fragment..." (page 1076, first quarter of right column). Dolferus did not show any data of mutations in regions outside the identified sequence elements, but that mutations in essential regions affected promoter activity. Thus, Dolferus demonstrated through simple deletion experiments, in combination with a search for known or predicted promoter boxes, that a person of skill in the art could identify which regions or elements of the promoter are essential for preserving function and any mutations in the essential elements would affect activity.

All three references cited by the Examiner show that promoter fragments with a particular activity can be identified by standard deletion experiments, that essential sequence elements can be predicted and identified by sequence analysis, and that those sequence elements represent only a minor part of the promoter sequence. By showing which parts of the promoter sequence are essential through routine experimentation and that only small parts of the original promoter sequence are necessary for activity, Kim, Donald, and Dolferus demonstrate which parts of a promoter sequence can be changed, which substitutions can and cannot be made which will affect activity, and that the majority of a promoter sequence might be changed without losing promoter activity.

Additionally, the present application describes that the delimitation of the promoter sequence to certain essential regulatory regions can be carried out through routine search and experimentation (see specification at page 11, lines 9-18). Moreover the specification provides detailed guidance on determining promoter expression and activity, for example at page 11 line 33 through page 13 line 5, and page 37, lines 15-21. The specification provides detailed

guidance on cloning the promoters of the invention into a vector as exemplified in Example 2, on transformation as in Exampled 3, and testing for activity as in Examples 5, 6, and 7. Thus in view of Examples 2, 3, and 5-7, one skilled in the art would recognize that screening and testing for promoter activity is routine and is not undue experimentation. The same applies to screening and testing the promoter activity of fragments of the sequences as claimed in the present application, which techniques are also known to one of skill in the art (see Kim, Donald, and Dolferus cited by the Examiner). It is submitted that determining the functional activity is routine experimentation and not undue experimentation. Compare, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (routine screening of hybridomas was not "undue experimentation;" the involved experimentation can be considerable, so long as "routine"). The test for whether experimentation is "undue" is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (1982). In the present case, the specification provides detailed guidance and teaches in the Examples, as explained above, the types of routine assay which are employed to confirm the claimed activity and additionally working examples showing activity. The detailed guidance provided in the present specification and the routine nature of the screening for the claimed activity overcome the unpredictability alleged by the Examiner.

Thus, from a promoter sequence and a description of its promoter activity, a person of skill in the art can readily identify promoter fragments with a preserved promoter activity and the important sequence elements contained therein by using routine experimentation as described in the present application and as demonstrated by Kim, Donald, and Dolferus. Furthermore, the person of skill in the art can readily identify the majority of nucleotides in the promoter sequence which are not necessary for activity and which might be changed or deleted without losing the promoter activity. By using routine experimentation, a person skilled in the art would be readily able to construct sequence fragments and variants preserving the claimed promoter activity.

In view of the detailed description, guidance, working examples, and high level of skill, the specification enables the full scope of the present claims without undue experimentation. On

these facts, an analysis under *In re Wands* supports enablement. For these reasons and in light of the amendments, reconsideration and withdrawal of this rejection is respectfully urged.

Applicants note that claims reciting functional fragments of promoter sequences have been granted in numerous other applications, where obtaining functional fragments have been found to be routine for one of skill in the art.

Written Description Rejection

The Examiner alleges that the specification only describes SEQ ID NO: 1 but that the claims are drawn to a multitude of sequences and the specification does not provide a description of any smaller fragment or any embodiment of sequences containing substitutions, deletions or derivatives that would also function as promoters in the claimed invention. Applicants respectfully disagree. However, in order to expedite prosecution, the claims have been amended without prejudice or disclaimer and relate to using a promoter sequence or a fragment thereof for directing expression of a further nucleic acid sequence in carbohydrate-storing sink tissue of plants, but essentially not in source tissues. Applicants respectfully request reconsideration in light of the amendment and for the following reasons.

The applicable test for written description is stated in the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, Written Description Requirements" 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001). As there indicated, the written description requirement for a claimed genus can be satisfied in a number of alternative ways, such as through sufficient description of a representative number of species by actual reduction to practice, by disclosure of relevant identifying characteristics, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics.

In *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) cited by the Examiner, the Federal Circuit held that a "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs..." The specification provides three actual sequences, SEQ ID NO: 1, 2, and 3, of the promoter region of the gene encoding Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase.

Additionally, the specification shows in Examples 5-7 the directed expression of the promoter in plants. Because each embodiment need not be disclosed (see *In re Angstadt*), the specification provides a representative number of sequences under the standard of *Regents v. Lilly*. See *In re Angstadt*, 537 F.2d 498 (CCPA 1976) (holding that there has never been a requirement that every species encompassed by a claim must be disclosed or exemplified in a working example).

The Examiner also bases the written description rejection on the invention allegedly being described solely in terms of a method of its making coupled with function citing MPEP § 2163, or in terms of the invention not being reduced to practice until defined by "its physical or chemical properties" (*e.g.* a DNA sequence) citing *Amgen v. Chugai*, 18 U.S.P.Q.2d 1601 (Fed. Cir. 1993). In the present application, the specification discloses at least three actual sequences, SEQ ID NO: 1, 2, and 3, of the promoter region of the gene encoding Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase, thereby providing a description of the DNA itself. Furthermore, in the present application, the nucleic acid sequences are not solely defined by function or by a general method for identifying or obtaining a promoter. Rather, three actual sequences are disclosed in the specification. Therefore, the MPEP section cited by the Examiner and *Amgen* are inapposite to the present application.

The specification therefore not only discloses a representative number of species, but additionally also provides the specific structures (by actual sequences) and specific activity of the promoter. Furthermore the claims require that the promoter sequence or fragment thereof direct expression to carbohydrate-storing sink tissue, but essentially not in source tissue, which has been exemplified in Examples 5-7.

For at least the above reasons, it is submitted that the amended claims have overcome the written description rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner rejects claims 1, 7, and 19-20 under 35 U.S.C. 102(b) as being anticipated by Barry *et al.* (US Patent 6,235,971; hereinafter "Barry"). Applicants respectfully disagree and traverse the rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegall Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). "[T]o hold that a prior art reference anticipates a claim, the Board must expressly find that every limitation in the claim was identically shown in the single reference." *Gechter v. Davidson*, 116 F.3d 1454, 1460 (Fed. Cir. 1997).

Applicants respectfully submit that Barry does not anticipate the present invention for the following reasons.

The Examiner has interpreted the promoter sequence to be as little as 2 base pairs or merely a TATAA box (see Office Action, pages 2 and 7). Applicants respectfully disagree with the Examiner's characterization, as explained above. For clarification the claims are amended without disclaimer or prejudice and are directed to a functional promoter or functional fragment thereof which directs expression of a nucleic acid to carbohydrate-storing sink tissue of plants. Thus, the promoter or fragment thereof must be capable of directing expression to carbohydrate-storing sink tissue, but essentially not in source tissue. A promoter comprising only a two base pair sequence or a TATAA box would not meet the claim limitations.

Furthermore, the claims recite that the promoter is a promoter sequence of the gene encoding the Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase. Barry does not disclose or mention the gene encoding the Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase or the promoter region of this gene. Since every limitation in the claim is not identically shown in Barry, Barry does not anticipate the claims.

The Examiner also alleges that Barry's teaching of a class I patatin promoter that comprises a TATAA box at the very least would be inherently a promoter sequence from the gene encoding the Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase. Applicants respectfully disagree.

For the Examiner to establish inherency, the rationale or evidence provided "must make clear that the missing descriptive matter is ***necessarily present*** in the thing described in the reference." *In re Robertson*, 169 F.3d 743, 745 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

First the promoter sequence from the gene encoding the Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase is not described or disclosed in Barry. Additionally, the claims require that the promoter sequence or fragment thereof be capable of directing expression to carbohydrate-storing sink tissue, but essentially not in source tissue. A TATAA box does not meet the claim limitations. Moreover, the Examiner has not made clear that any disclosure in Barry would necessarily comprise a functional promoter sequence or functional fragment thereof from the gene encoding the Vicia faba plastidic 1,4-α-D-glucan:phosphate α-D-glucosyltransferase.

Because Barry does not disclose all the limitation of the claims, Barry does not anticipate the claims. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims.

Accompanying this response is a petition for a two-month extension of time to and including March 3, 2008 pursuant to 37 CFR § 1.7(a) to respond to the Office Action mailed October 2, 2007 with the required fee authorization. No further fees are believed due. If any additional fee is due, the Director is hereby authorized to charge our Deposit Account No. 03-2775, under Order No. 13173-00008-US from which the undersigned is authorized to draw.

Respectfully submitted,

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